The Modern Epidemic of Syphilis

Ghanem KG, Ram S, Rice PA

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Several at-risk populations are more commonly infected with syphilis than others, and the current incidence of syphilis is being called an epidemic. A marked increase in syphilis has been seen in homosexual men, and more than half of men with syphilis report having sex with men. About 40 percent of those men are infected with the human immunodeficiency virus (HIV), but the current epidemic also affects heterosexual men and women, with the rate of primary and secondary syphilis in this segment having doubled between 2014 and 2018. The incidence of syphilis has risen markedly in women who use methamphetamine, heroin, and other injectable drugs.

Syphilis is caused by a spirochete, Treponema pallidum. The initial infection produces an open but painless skin ulcer, termed a chancre. The lesion is solitary, indurated, and has a clean base. The primary syphilis lesion occurs at the site contacted by an infected individual, usually the genitals but also the perirectal area, rectum, or mouth. Secondary syphilis produces a mild nonpruritic skin rash, often on the palms or soles. The secondary phase can also produce a fever or lymphadenopathy. Adenopathy often prompts a patient to seek medical care, and it should be looked at carefully.

Primary and secondary syphilis are often missed or misdiagnosed because the symptoms suggest such a wide differential diagnosis. Diagnosing syphilis is done with serologic tests, and there are quite complicated. Numerous versions exist, and interpretation is not that easy. T. pallidum cannot be grown in the laboratory, so no culture tests are available, and no test directly detects the organism. A test looking for the organism in an ulcer, called the dark field microscopic examination, was previously used, but is no longer available.

Two basic screening tests are available, treponemal and nontreponemal, and both should be performed. The standard basic screening test, a nontreponemal test called a rapid plasma reagin test (RPR), or the venereal disease research laboratory test (VDRL) can be performed rapidly and done on ED patients with some cautioning and usually difficult-to-obtain cooperation from the hospital laboratory. This test is confirmed with a highly specific and more sensitive treponemal test. The RPR and VDRL tests are reported as a ratio, such as 1:32, and it changes over time and decreases with treatment.

A treponemal test, such as the fluorescent treponemal antibody absorption test (FTA-ABS), confirms the first test, and is reported as positive or negative. This test remains positive for a patient’s lifetime and does not change with treatment. The first test can have some false positives, especially if the ratio is small, such as 1:4. The test can be used to assess response to therapy because it decreases with successful treatment. Patients who have a positive nontreponemal test followed by a negative treponemal test are generally considered to have a false-positive syphilis result. Both tests are required, but either one can be done first. The RPR and VDRL tests are usually done first because the laboratory can perform them on ED patients.

Penicillin is the drug of choice for syphilis, and it is highly effective. Resistance has not been observed. Uncomplicated primary and secondary syphilis, including HIV-infected adults, are treated with a single dose of 2.4 million units of long-acting penicillin G benzathine, given intramuscularly. Note that this is Bicillin L-A, not Bicillin C-R, a combination of procaine and benzathine penicillin, that should not be used. It recently had a label applied to the syringe stating that it should not be used for syphilis, and the nursing staff should be educated about that.

Late syphilis is treated with three doses of penicillin G benzathine, 2.4 million units intramuscularly, at weekly intervals. Desensitization and treatment with penicillin are recommended for patients with documented penicillin allergy. An alternative is tetracycline 100 mg twice a day for 28 days if penicillin is absolutely contraindicated. A second alternative is ceftriaxone 1-2 q daily IM for 10-14 days. Late syphilis, latent syphilis, neurosyphilis, cardiovascular syphilis, and ocular syphilis have alternate dosing, and it is best to consult a specialist for these patients. Syphilis has likely become such a widespread problem because it is such a complicated disease.

Managing Persons Who Have a History of Penicillin Allergy

Sexually Transmitted Infections Treatment Guidelines

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Penicillin is recommended for treating all clinical stages of syphilis, and
some alternatives treat early stages, but no proven alternatives exist for neurosyphilis, congenital syphilis, or syphilis during pregnancy. The reported prevalence of penicillin allergy is approximately 10 percent in the United States. It is generally agreed that penicillin allergy is the most frequently reported antibiotic allergy, but it is overreported and the majority of patients reporting it can actually tolerate it. Penicillin allergy concerns lead to the use of more expensive and less effective drugs and can result in adverse consequences. Allergy wanes, and patients with remote reactions might no longer be reactive. Validated penicillin allergy is proven in fewer than 10 percent of those reporting allergy.

Penicillin and cephalosporins contain a β-lactam ring and patients with a penicillin allergy are often precluded from treatment with a cephalosporin. Cephalosporin allergy has a cross reaction of about five to eight percent with first-generation cephalosporins, but cross reactivity is less than one percent with third-generation cephalosporins, such as ceftriaxone. Penicillin is such an important antibiotic for treating all forms of syphilis that those reporting an allergy should be tested for a true allergy. Testing involves three steps, and is generally not initiated in the ED. If no alternative is available, testing and desensitization are advised. These interventions are complicated and usually performed by an allergist. A patient who says he has an allergy to penicillin should not be treated with the drug unless tested by an allergist. Tetracycline, 100 mg BID for 28 days, seems to be as effective as penicillin, but data are sparse. Ceftriaxone has been shown to have efficacy similar to penicillin in all stages of syphilis, but data are from only observational studies. Ceftriaxone penetrates into the CNS and is an option for neurosyphilis if penicillin desensitization is not possible. Minimal data are available on the use of ampicillin and amoxicillin; these may be effective, but cannot be used in patients allergic to penicillin. Azithromycin and other macrolides are not currently recommended because resistance has been reported.

The emergency physician should be able to conduct screening and initial diagnostic testing of patients who may have syphilis, but it is best to involve a consultant for anything other than diagnosing syphilis and treating new uncomplicated cases. Follow-up, usually in six to 12 months, is suggested for even a basic case. An infectious disease specialist is the most likely first consultant. All those suspected of having syphilis should also have HIV testing and be examined for other sexually transmitted infections. Pregnancy presents a number of issues, and a consultant is best used when treating pregnant patients. Those with neurosyphilis, the elderly, patients with HIV, or those with a previous diagnosis should also be referred to a consultant.

How Is Syphilis Transmitted?
Transmission of *T. pallidum* usually occurs via direct contact with an infected lesion during sex. Acquiring syphilis through transfused blood is rare because all donors are screened and *T. pallidum* cannot survive longer than 24 to 48 hours under blood bank storage conditions. The bacterium also crosses the placenta and results in fetal infection. Sexual transmission requires exposure to open lesions with the organism present.

The median incubation period before the chancre appears is two to three weeks after exposure. Some of the manifestations of secondary syphilis (mucous patches and condyloma lata) can transmit the disease. These lesions are very infectious, with an efficiency of transmission estimated at approximately 30 percent. Syphilis can be spread by kissing or touching a person who has active lesions on the lips, breasts, and genitals or in the mouth.

Who Should Be Treated?
Initial treatment decisions are often difficult, laboratory tests lacking, and follow-up notoriously difficult. The emergency physician must often treat based on minimal evidence and a lot of hope that the medical system will help after the ED visit. Treatment is rather benign, so penicillin can be justified with minimal supporting data. Certain groups of patients can be treated empirically for early syphilis based on clinical findings, such as a suspected chancre, a rash on the palms or soles, diffuse adenopathy, or a known recent exposure. An initial blood test should always be analyzed. Be certain that IM penicillin G benzathine (*Bicillin L-A*) is used, not *Bicillin C-R*. Follow-up is suggested, but can be difficult. The physician should be familiar with available follow-up options, and another nontreponemal blood test should be performed in six months to document a fourfold or greater decrease in titers, such as from 1:32 to 1:18.

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**Learning Objectives for This Month’s CME Activity:** After participating in this CME activity, readers should be better able to explain how to diagnose and initially treat syphilis.

Dr. Roberts is a professor of emergency medicine and toxicology at the Drexel University College of Medicine in Philadelphia. Read his past columns at http://bit.ly/EMN-InFocus.